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54 Novel androstane-17 beta-carboxylic acid esters, a process and intermediates for their preparation, composition and method for the treatment of inflammatory conditions.

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73 Proprietor: Aktiebolaget Draco
Box 34
S-221 00 Lund (SE)

72 Inventor: Brattsand, Ralph Lennart
Skolmästarvägen 4
S-223 67 Lund (SE)
Inventor: Thalén, Bror Arne
Morkullevägen 35
S-237 00 Bjärred (SE)

74 Representative: Hjertman, Ivan T. et al
AB ASTRA Patent and Trade Mark Department
S-151 85 Södertälje (SE)

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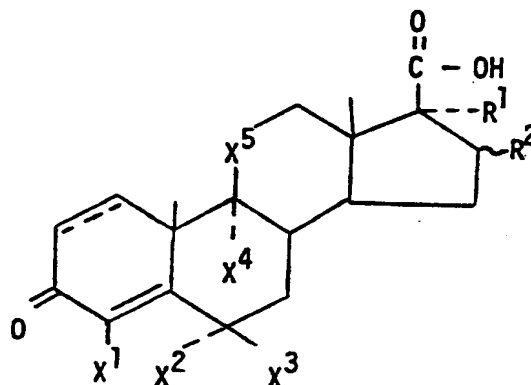
Description

The present invention relates to novel, pharmacologically active compounds and a process and intermediates for their preparation. The invention also relates to pharmaceutical compositions containing the compounds and to methods of treatment of inflammatory conditions with these compounds.

The object of the invention is to provide a glucocorticosteroid which possesses a combination of high anti-inflammatory potency on the place of application and low glucocorticoid systemic potency.

It is known that certain glucocorticoids (GCS) can be used for local therapy of inflammatory, allergic or immunologic diseases in respiratory airways (e.g. asthma, rhinitis), in skin (eczema, psoriasis) or in bowel (ulcerative colitis, Morbus Crohn). With such local glucocorticoid therapy, clinical advantages over general therapy (with e.g. glucocorticoid tablets) are obtained, especially regarding reduction of the unwanted glucocorticoid effects outside the diseased area. To reach such clinical advantages, in e.g. severe respiratory airway disease, GCS must have a suitable pharmacological profile. They should have a combination of high intrinsic glucocorticoid activity of the application site but also a rapid inactivation by biotransformation (e.g. in the liver) after uptake into the general circulation. In laboratory models, the intrinsic glucocorticoid activity can be measured as local anti-inflammatory potency on the rat ear and the unwanted systemic glucocorticoid activity determined from the extent of thymus involution.

From the literature compounds of the formula



wherein

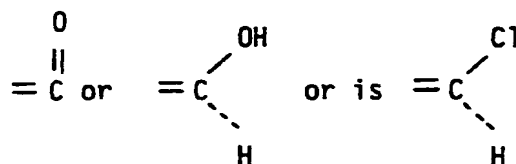
X¹ is hydrogen, fluoro, chloro or bromo;

X² is hydrogen, fluoro or chloro;

X³ is hydrogen or is fluoro when X² is fluoro and X¹ is hydrogen;

X⁴ is hydrogen, fluoro, chloro or bromo;

X⁵ is



when X⁴ is chloro;

X⁴ and X⁵ together represent an additional bond between C-9 and C-11;

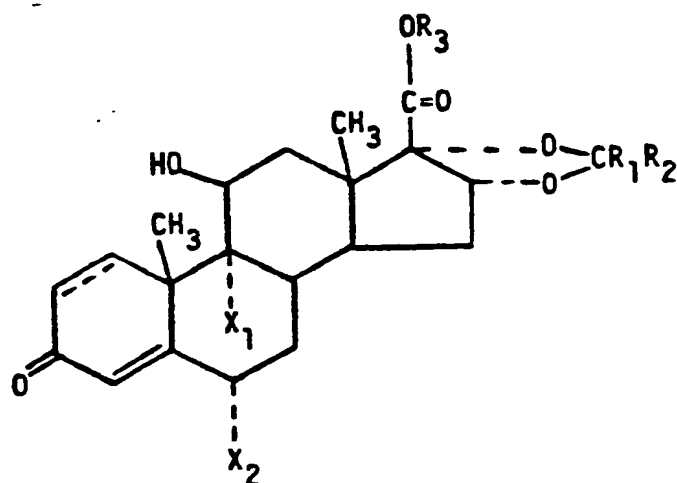
R¹ is hydroxy or is alkanoyloxy of 2-6 carbons when R² is α-methyl, β-methyl or hydrogen;

R¹ and R² together are isopropylidenedioxy; and the solid and broken lines between C-1 and C-2 represent a single or double bond, are known (US-A-4 198 336). These compounds are said to be useful as topical anti-inflammatory agents.

The present invention is based on the observation that certain 3-oxo-androst-4-ene and 3-oxoandrost-1,4-diene-17³-carboxylic acid esters possess anti-inflammatory potency on the place of application in combination with very low glucocorticoid systemic effects. The compounds of the invention can be used for the treatment and control of inflammatory conditions.

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The compounds of the invention are characterized by the formula



(I)

wherein the 1,2-position is saturated or is a double bond

X₁ is selected from hydrogen, fluorine, chlorine and bromine

X₂ is selected from hydrogen, fluorine, chlorine and bromine

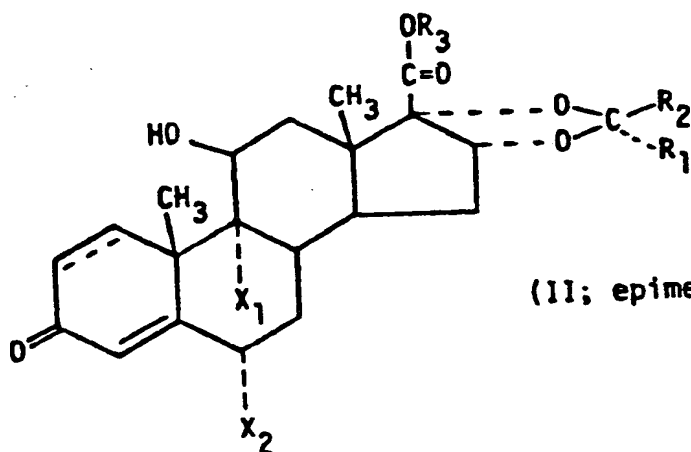
R₁ is selected from hydrogen

R₂ is selected from straight and branched hydrocarbon chains having 1—10 carbon atoms and

R₃ represents straight chain or branched alkyl group having 1—12 carbon atoms or a lower alkyl group (1—5 carbon atoms) substituted by 1—5 halogen atoms.

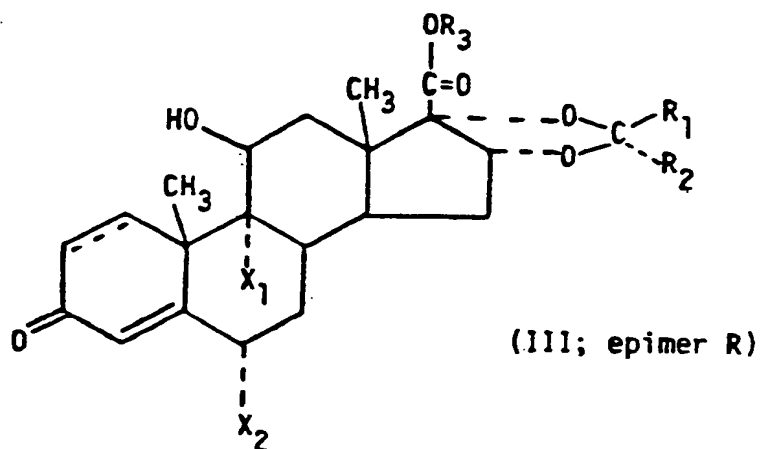
Halogen is chlorine, fluorine or bromine.

The individual stereoisomeric components present in a mixture of a steroid having the above formula (I) can be elucidated in the following way:



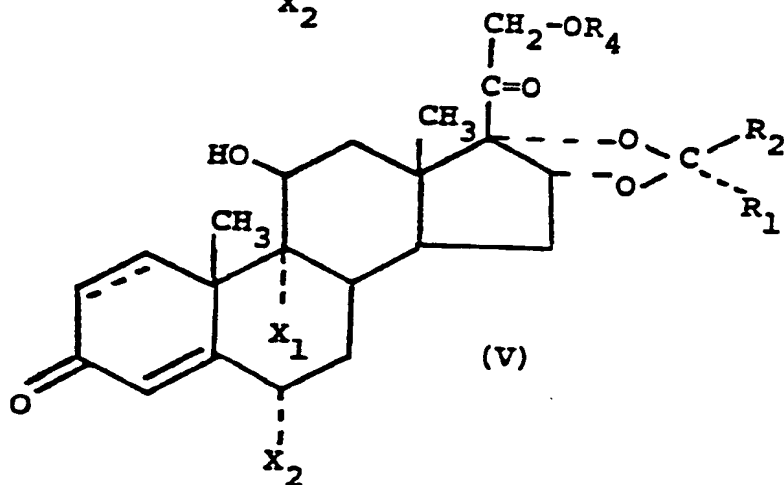
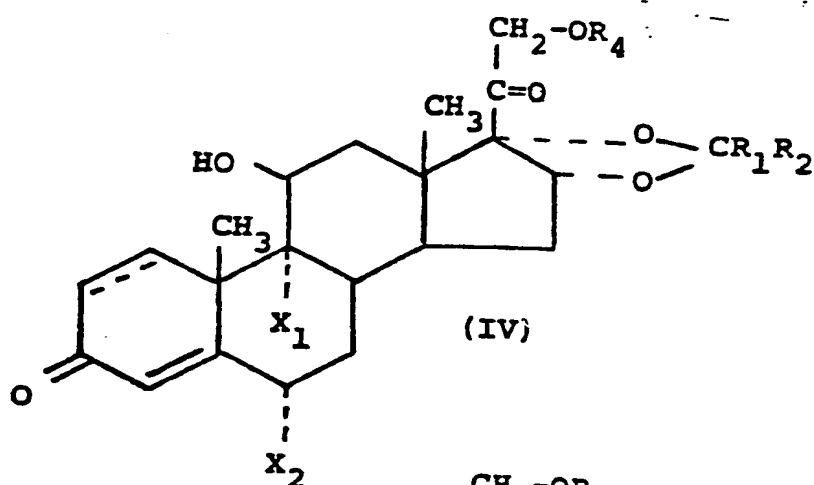
(II; epimer S)

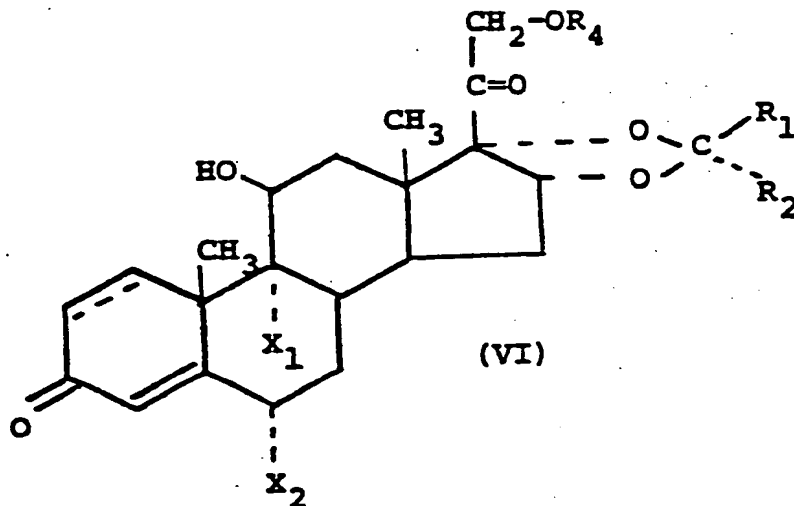
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In diastereoisomers like II and III, the configuration differs only at one (C-20) out of several asymmetric carbon atoms. Such diastereoisomers are denoted epimers.

The compounds of the invention are prepared by the oxidation of a compound of structure IV, V and VI to the corresponding 17 β -carboxylic acid:





wherein the solid and broken lines between C—1 and C—2 represent a single or double bond, X_1 , X_2 , R_1 and R_2 have the meaning given above, and R_4 is hydrogen or —OC-alkyl, wherein the alkyl moiety has 1—5 carbon atoms.

The 17 β -carboxylic acids then are esterified to give compounds characterized by the formula I, II and III, wherein —, X_1 , X_2 , R_1 , R_2 and R_3 have the meaning given above.

The process of this invention to convert a compound of formulas IV, V or VI to the corresponding 17 β -carboxylic acids is carried out in a suitable oxygenated hydrocarbon solvent such as a lower alkanol. Methanol and ethanol are preferred, particularly the former. The reaction medium is made slightly alkaline by the addition of a suitable weak inorganic base such as an alkali metal carbonate, for example sodium, lithium or potassium carbonate. The latter is preferred. The conversion of a compound of formula IV, V or VI to a 17 β -carboxylic acid of formula I, II and III takes place at ambient temperatures, i.e. 20—25°C.

The presence of oxygen is necessary for the reaction. Oxygen can be supplied by bubbling a stream of air or oxygen into the reaction mixture.

The oxidative degradation of the 17 β side-chain of compounds of formula IV, V and VI to the corresponding 17 β -carboxylic acids can also be carried out with periodic acid or with sodium bismuthate. The reaction is performed in a mixture of water and a suitable oxygenated hydrocarbon solvent such as a lower ether. Dioxane and tetrahydrofurane are preferred, particularly the former.

The parent 17 β -carboxylic acids of compounds of formula I, II and III may be esterified in known manner to provide 17 β -carboxylate esters according to the invention. For example, in order to prepare a lower alkyl ester, the 17 β -carboxylic acid may be reacted with an appropriate diazoalkane, e.g. diazomethane, the reaction being preferably performed in a solvent medium, e.g. ether, tetrahydrofurane or methanol, and at a low temperature preferably at —5°C to +30°C. Alternatively, the 17 β -carboxylic acid may be reacted with an appropriate alcohol and a carbodiimide, e.g. dicyclohexylcarbodiimide, in a suitable solvent such as diethylether, tetrahydrofurane, methylene chloride or pyridine advantageously at a temperature of 25—100°C. Alternatively, a salt of the 17 β -carboxylic acid with an alkali metal, e.g. lithium, sodium or potassium, a salt of a quaternary ammonium compound, e.g. tetrabutylammonium, may be reacted with an appropriate alkylating agent, for example an alkyl halide or dialkylsulfate, e.g. dimethylsulfate, preferably in a polar solvent medium such as acetone, methylethylketone or dimethylformamide, conveniently at a temperature in the range 25—100°C.

The crude steroid ester derivatives formed are after isolation purified by chromatography on a suitable material, for instance cross-linked dextran gels of Sephadex® LH-type with suitable solvents as eluants, e.g. halogenated hydrocarbons, ethers, esters such as ethyl acetate or acetonitrile.

The individual 20R and 20S epimers, which are formed at the esterification with the epimeric mixtures of the acids, possess practically identical solubility characteristics. Accordingly, they have turned out to be impossible to separate and isolate from the epimeric mixture by conventional method for resolution of stereoisomers, e.g. fractionated crystallization. The process according to the invention consists in subjecting stereoisomeric mixtures according to the formula (I) above to column chromatography, the epimers 20R and 20S being separated in view of different mobility on the stationary phase, why they can be separately recovered. The chromatography may be carried out for instance on alkylsilanes or cyanoalkylsilanes of the type μ Bondapak® C₁₈ and μ Bondapak CN in combination with a suitable mixture of organic solvents or a mixture of organic solvents and water as eluting agent. μ Bondapak C₁₈ is a octadecylsilane bonded phase and μ Bondapak CN is a cyanopropylsilane bonded phase prepared by Waters Associates, USA. As mobile phase a mixture of ethanol or methanol and water in the proportions 30—70:70:30 or heptane and ethanol in the proportions 80—100:0—20, respectively has successfully been used.

The compounds of the invention may be used for different modes of local administration dependent on the site of inflammation, e.g. percutaneously, parenterally or for local administration in the respiratory tract by inhalation. An important aim of the formulation design is to reach optimal bioavailability of the active steroid ingredient. For percutaneous formulations this is advantageously achieved if the steroid is dissolved with a high thermodynamic activity in the vehicle. This is attained by using a suitable system of solvents comprising suitable glycols, such as propylene glycols, such as propylene glycol or 1,3-butandiol either as such or in combination with water. It is also possible to dissolve the steroid either completely or partially in a lipophilic phase with the aid of a surfactant as a solubilizer. The percutaneous compositions can be an ointment, an oil in water cream, a water in oil cream or a lotion. In the emulsion vehicles the system comprising the dissolved active component can make up the disperse phase as well as the continuous one. The steroid can also exist in the above compositions as a micronized, solid substance.

Aerosols for steroids are intended for oral or nasal inhalation. The aerosol system is designed in such a way that each delivered dose contains 10—1000 µg, preferably 20—250 µg of the active steroid. The most active steroids are administered in the lower part of the dosage range. The micronized steroid consists of particles substantially smaller than 5 µm. In the pressurized aerosol the substance is suspended in a propellant gas mixture with the assistance of a dispersant, such as sorbitan trioleate, oleic acid, lecithin or sodium salt of dioctylsulphosuccinic acid.

The invention will be further illustrated by the following non-limitative examples. In the examples a flow-rate of 2.5 ml/cm² · h⁻¹ is used at the preparative chromatographic runs. Molecular weights are in all examples determined with electron impact mass spectrometry and the melting points on a Leitz Wetzlar hot stage microscope. All HPLC analyses (HPLC = High Performance Liquid Chromatography) were, if not otherwise stated, performed on a Waters µBondapak C₁₈ column (300 × 3.9 mm internal diameter) with a flow-rate of 1.0 ml/min and with ethanol-water in ratios between 50:50 and 60:40 as mobile phase, if not otherwise stated.

Example 1

This example sets forth a process for preparing (20RS)-, (20R)- and (20S)-11β-hydroxy-16α,17α-alkylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylic and -androsta-4-ene-3-one-17β-carboxylic acids.

Preparation of (20RS)-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylic acid.

A. To a solution of 1.00 g of (22RS)-11β,21-dihydroxy-16α,17α-propylmethylenedioxypregna-1,4-diene-3,20-dione in 195 ml of ethanol 90 ml of 1% aqueous potassium carbonate was added. A stream of air was bubbled through this solution for about 20 h under stirring at room temperature. The ethanol was evaporated and 100 ml of water was added to the residue. This mixture was acidified with concentrated hydrochloric acid to pH 2 and extracted with ethyl acetate. The extracts were washed with 10% aqueous potassium carbonate. The aqueous phase was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. After drying the solvent was evaporated and 3 ml of acetone was added to the residue. The precipitate formed was collected by filtration and dried to yield 742 mg of (20RS)-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylic acid, melting point 126—30°C, molecular weight 416. Purity: 97.3% (HPLC: 0.01 M acetic acid, 44:56); epimer 20R:20S, 85:15.

B. Periodic acid (575 mg) in 2 ml of water was added to a solution of (22RS)-11β,21-dihydroxy-16α,17α-propylmethylenedioxypregna-1,4-diene-3,20-dione in 7 ml of dioxane. The reaction mixture was stirred at room temperature of 4.5 h, neutralized with saturated aqueous sodium hydrogen carbonate and evaporated. The residue was dissolved in 60 ml of methylene chloride and washed with 6 × 25 ml 10% aqueous potassium carbonate. The aqueous phase was acidified with conc. hydrochloric acid and extracted with 4 × 50 ml of ethyl acetate. After drying the solvent was evaporated. The residue was dissolved in a small amount of ethyl acetate and precipitated with petroleum ether yielding 720 mg of (20RS)-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylic acid. The purity determined by HPLC was 97.8% and the ratio epimer 20R:20S was 45:55.

C. Preparation of (20R)-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylic acid.

To a solution of 1.00 g of (22R)-21-acetoxy-11β-hydroxy-16α,17α-propylmethylenedioxypregna-1,4-diene-3,20-dione in 150 ml of ethanol 150 ml of 10% aqueous potassium carbonate was added. A stream of air was bubbled through the solution for about 20 h under stirring at room temperature. The reaction mixture was worked up as in procedure A and precipitated from ethyl acetate — petroleum ether yielding 707 mg of (20R)-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylic acid.

D. Preparation of (20S)-11β-hydroxy-16α,17α-propyl-methylenedioxyandrosta-1,4-diene-3-one-17β-carboxylic acid.

To a solution of 1.00 g of (22S)-21-acetoxy-11β-hydroxy-16α,17α-propylmethylenedioxypregna-1,4-diene-3,20-dione in 150 ml of ethanol 150 ml of 10% aqueous potassium carbonate was added. A stream of air was bubbled through the solution for about 40 h under stirring at room temperature. The reaction mixture was worked up as in procedure A and precipitated from ethyl acetate — petroleum ether yielding

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617 mg of (20S)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylic acid.

5 E. Similarly, by following the procedure set forth in the example by substituting the 16 α ,17 α -acetal between 16 α -hydroxyprednisolone, triamcinolone and fluocinolone and acetaldehyde, propanol, butanal, isobutanal, pentanal, 3-methylbutanal, 2,2-dimethylpropanal, hexanal, heptanal, octanal, nonanal and dodecanal and their 21-esters (20RS)- (20R)- and (20S)-11 β -hydroxy-16 α ,17 α -alkyl-
10 methylenedioxyandrosta-1,4-diene- and 4-ene-3-one-17 β -carboxylic acids are prepared (see Table 1 below).

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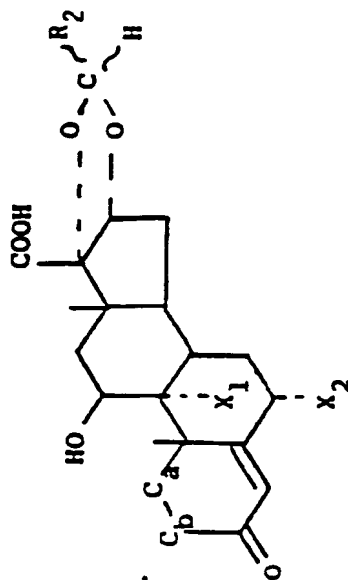
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Table 1



C_a-C_b	X_1	X_2	R_2	Epimer	Yield (%)	Mp. (°C)	Molecular weight calculated	Molecular weight found
$-CH=CH-$	H	H	CH_3	20R+S	96		388.5	
$-CH_2-CH_2-$	H	H	$(CH_2)_2CH_3$	20R+S	78		418.5	
$-CH_2-CH_2-$	H	H	$(CH_2)_2CH_3$	20R	62		418.5	
$-CH=CH-$	F	H	$(CH_2)_2CH_3$	20S	76	199-224	434.5	434
$-CH=CH-$	F	H	$(CH_2)_2CH_3$	20R	80	220-41	434.5	434
$-CH=CH-$	F	F	$(CH_2)_2CH_3$	20R	89		452.5	
$-CH=CH-$	H	H	$(CH_2)_4CH_3$	20S	85		444.6	
$-CH=CH-$	H	H	$(CH_2)_4CH_3$	20R	98		444.6	

⊕ Where no data is given the compounds have been used as intermediates for the preparation of the corresponding esters without further analysis.

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Example 2

Methyl (20RS)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate. (20RS)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylic acid (500 mg) and 611 mg of tetrabutylammonium hydrogen sulphate were added to 3 ml of 1M sodium hydroxide.

A solution of 1 ml of methyl iodide in 20 ml of methylene chloride was added. The mixture was refluxed with stirring for 1 h. The two layers were separated. The methylene chloride solution was dried and evaporated to a volume of 5 ml and 25 ml of ether was added to precipitate the tetrabutylammonium iodide which was removed by filtration. The solvents were evaporated and the residue purified by chromatography on a Sephadex® LH-20 column (72 x 6.3 cm) using chloroform as eluant. The fraction 1320—1545 ml was collected and evaporated yielding 289 mg of methyl(20RS)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate. The purity determined by HPLC was 99.8% and the ratio epimer 20R:20S, 49.6:50.4 (μ Bondapak CN column, heptane: ethanol, 95:5). Melting point: 128—91°C.

$[\alpha]_D^{25} = +80^\circ\text{C}$ (c=0.200; CH₂Cl₂). The molecular weight was 430.

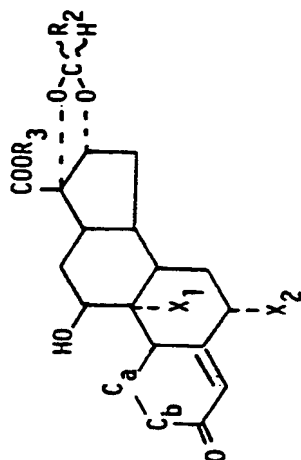
(20RS)-11 β -Hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylic acid (100 mg) and methanol (0.01 ml) were added to 5 ml of dry pyridine. p-Toluenesulphonic acid (2 mg) was added and the mixture stirred for 15 min. Dicyclohexylcarbodiimide (60 mg) was added and the mixture was stirred at room temperature for 24 h. Acetic acid (0.2 ml) was added and the reaction mixture was kept overnight at 4°C. The precipitate formed was removed by filtration. Methylene chloride (16 ml) and ice (8 g) was added to the filtrate and 5M hydrochloric acid was then added with stirring until pH 2.5 was reached. The organic layer was washed with water, saturated sodium hydrogen carbonate and water, dried and evaporated. The residue was purified by chromatography on a Sephadex® LH-20 column (72 x 6.3 cm) using chloroform as eluant. The fraction 1455—1620 ml was collected and evaporated. The residue was dissolved in methylene chloride. Precipitation with petroleum ether yielded 27 mg of methyl (20RS)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate. The purity determined by HPLC was 99.5%. The ratio epimer 20R:20S was 51.2:48.8 (determined by HPLC, μ Bondapak CN column, heptane:ethanol, 95:5).

(20RS)-11 β -Hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylic acid (42 mg) and potassium hydrogen carbonate (10 mg) were dissolved in 10 ml of dimethyl formamide. A solution of 21 mg of methyl iodide in 5 ml of dimethyl formamide was added and the reaction mixture stirred at room temperature overnight. Water (50 ml) was added and the mixture was extracted with methylene chloride. The combined extracts were washed with 5% aqueous sodium hydrogen carbonate and water, dried and evaporated. A yield of 26 mg of methyl(20RS)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate was obtained. The purity determined by HPLC was 98.5%.

Examples 3—11

The substances given in Table 2 below were prepared, isolated and purified in a manner analogous to that described in Example 2.

Table 2



Example No.	C _a -C _b	X ₁	X ₂	R ₂	R ₃	M.p. °C	[α] _D ²⁵ (c=0.2 in CH ₂ Cl ₂)	Molecular weight found	Retention volume ¹⁾ (ml)
3	-CH=CH-	H	H	CH ₃	CH ₃	212-41	+ 89°	402	1545-1815
4	-CH ₂ -CH ₂ -	H	H	(CH ₂) ₂ CH ₃	CH ₃	110-47	+115°	432	1335-1530
5	-CH=CH-	F	H	(CH ₂) ₂ CH ₃	CH ₃	204-10	+ 77°	448	1980-2235
6	-CH=CH-	H	H	(CH ₂) ₂ CH ₃	CH ₂ CH ₃	163-74	+ 77°	444	1380-1620
7	-CH=CH-	F	H	(CH ₂) ₂ CH ₃	CH ₂ CH ₃	210-42	+ 74°	462	1815-2115
8	-CH=CH-	H	H	(CH ₂) ₂ CH ₃	(CH ₂) ₃ CH ₃	147-59	+ 83°	472	1260-1485
9	-CH=CH-	H	H	(CH ₂) ₂ CH ₃	C(CH ₃) ₃	174-204		472	1530-1770
10	-CH=CH-	H	H	(CH ₂) ₂ CH ₃	CH ₂ Cl	186-90	+ 76°	464	1575-1860
11	-CH=CH-	H	H	(CH ₂) ₄ CH ₃	CH ₃	152-77	+ 73°	458	1425-1680

1) On a Sephadex LH-20 column (72x6.3 cm) using chloroform as eluant

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Example 12

Methyl(20R)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate.
(20R)-11 β -Hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylic acid (500 mg) and 611 mg of tetrabutylammonium hydrogen sulphate were added to 3 ml of 1M sodium hydroxide. A solution of 1 ml of methyl iodide in 20 ml of methylene chloride was added. The mixture was refluxed with stirring for 1 h. The two layers were separated. The methylene chloride solution was dried and the volume reduced to 5 ml. Ether (25 ml) was added to precipitate the tetrabutylammonium iodide, which was removed by filtration. The solvents were evaporated and the residue purified by chromatography on a Sephadex[®] LH-20 column (72 x 6.3 cm) using chloroform as eluant. The fraction 1395—1665 ml was collected and evaporated yielding 295 mg of methyl(20R)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate. The purity determined by HPLC was 99.1%.
Melting point: 210—14°C. $[\alpha]_D^{25} = +82^\circ\text{C}$ (c=0.266; CH₂Cl₂). The molecular weight was 430.

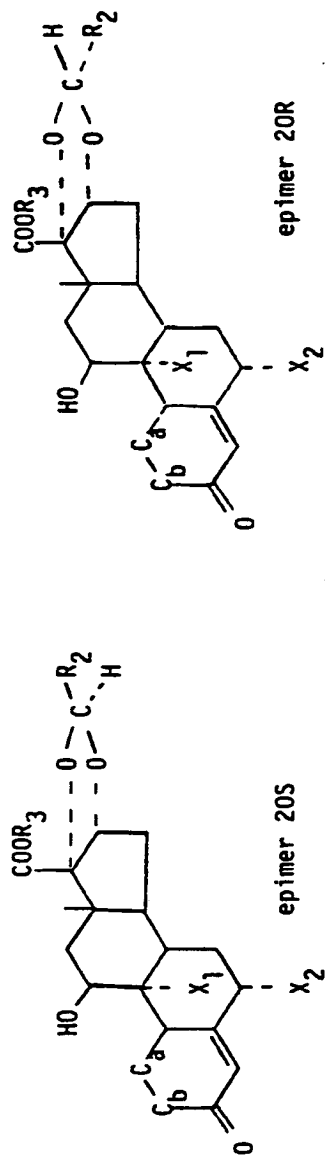
Example 13

Methyl (20S)-11 β -Hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate.
(20S)-11 β -Hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylic acid (617 mg) and 754 tetrabutylammonium hydrogen sulphate were added to 3.7 ml of 1M sodium hydroxide. A solution of 1M of methyl iodide in 20 ml of methylene chloride was added. The reaction mixture was refluxed with stirring for 1 h and isolated as in Example 11. The crude product was purified by chromatography on a Sephadex[®] LH-20 column (72 x 6.3 cm) using chloroform as eluant. The fraction 1440—1725 ml was collected and evaporated yielding 377 mg of methyl (20S)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate. The purity determined by HPLC was 99.3%.
Melting point: 175—84°C. $[\alpha]_D^{25} = +72^\circ\text{C}$ (C=0.232; CH₂Cl₂). The molecular weight was 430.

Examples 14—19

The substances given in Table 3 below were prepared, isolated and purified in a manner analogous to that described in Examples 12 and 13.

Table 3



Example No.	C _a -C _b	X ₁	X ₂	R ₂	R ₃	Epimer	Mp °C	$[\alpha]_D^{25}$ (c=0.2 in CH ₂ Cl ₂)	Molecular weight calc. found	Retention volume l) (ml)
14	-CH ₂ -CH ₂ -	H	H	(CH ₂) ₂ CH ₃	CH ₃	20R	166-74	+128°	432.6 432	1350-1560
15	-CH=CH-	F	H	(CH ₂) ₂ CH ₃	CH ₃	20S	260-63	+69°	448.5 448	1920-2220
16	-CH=CH-	F	H	(CH ₂) ₂ CH ₃	CH ₃	20R	209-10	+78°	448.5 448	1980-2160
17	-CH=CH-	F	F	(CH ₂) ₂ CH ₃	CH ₃	20R	223-26		466.5 466	430-95 2)
18	-CH=CH-	H	H	(CH ₂) ₄ CH ₃	CH ₃	20S	197-203	+67°	458.6 458	1425-1680
19	-CH=CH-	H	H	(CH ₂) ₄ CH ₃	CH ₃	20R	190-93	+79°	458.6 458	1425-1635

1) On a Sephadex LH-20 column (72x6.3 cm) using chloroform as eluant.

2) On a Sephadex LH-20 column (83x2.5 cm) using chloroform as eluant.

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Example 20, Pharmaceutical preparations

The following non-limitative examples illustrate formulations intended for different topical forms of administration. The amount of active steroid in the percutaneous formulations are ordinarily 0.001—0.2% (w/w), preferably 0.01—0.1 (w/w).

5 Formulation 1, Ointment

	Steroid, micronized	0.025 g
10	Liquid paraffin	10.0 g
	White soft paraffin	ad 100.0 g

15 Formulation 2, Ointment

	Steroid	0.025 g
	Propylene glycol	5.0 g
20	Sorbitan sesquioleate	5.0 g
	Liquid paraffin	10.0 g
	White soft paraffin	ad 100.0 g

25 Formulation 3, Oil in water cream

	Steroid	0.025 g
30	Cetanol	5.0 g
	Glyceryl monostearate	5.0 g
	Liquid paraffin	10.0 g
35	Cetomacrogol® 1000	2.0 g
	Citric acid	0.1 g
	Sodium citrate	0.2 g
40	Propylene glycol	35.0 g
	Water	ad 100.0 g

45 Formulation 4, Oil in water cream

	Steroid, micronized	0.025 g
	White soft paraffin	15.0 g
50	Liquid paraffin	5.0 g
	Cetanol	5.0 g
	Sorbimacrogol® stearate	2.0 g
55	Sorbitan monostearate	0.5 g
	Sorbic acid	0.2 g
60	Citric acid	0.1 g
	Sodium citrate	0.2 g
	Water	ad 100.0 g

EP 0 143 764 B1**Formulation 5, Water in oil cream**

	Steroid	0.025 g
5	White soft paraffin	35.0 g
	Liquid paraffin	5.0 g
10	Sorbitan sesquioleate	0.5 g
	Sorbic acid	0.2 g
	Citric acid	0.1 g
15	Sodium citrate	0.2 g
	Water	ad 100.0 g

Formulation 6, Lotion

20	Steroid	0.25 mg
	Isopropanol	0.5 ml
25	Carboxyvinylpolymer	3 mg
	NaOH	q.s.
30	Water	ad 1.0 g

Formulation 7, Suspension for injection

	Steroid, micronized	0.05—10 mg
35	Sodium carboxymethylcellulose	7 mg
	NaCl	7 mg
40	Polyoxyethylene (20) sorbitan monooleate	0.5 mg
	Phenyl carbinol	8 mg
	Water, sterile	ad 1.0 ml

Formulation 8, Pressurized aerosol for oral and nasal inhalation

	Steroid, micronized	0.1% w/w
50	Sorbitan trioleate	0.7% w/w
	Trichlorofluoromethane	24.8% w/w
	Dichlorotetrafluoromethane	24.8% w/w
55	Dichlorodifluoromethane	49.6% w/w

Formulation 9, Solution for atomization

60	Steroid	7.0 mg
	Propylene glycol	5.0 g
	Water	ad 10.0 g

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Formulation 10, Powder for inhalation

A gelatin capsule is filled with a mixture of

5	Steroid, micronized	0.1 mg
	Lactose	20 mg

The powder is inhaled by means of an inhalation device.

Pharmacological tests

All steroids according to the present invention are physiologically active compounds. The glucocorticoid properties of the compounds have been compared with those of budesonide ([22R,S]-16 α ,17 α -butylidenedioxy-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione) as this compound is one of the glucocorticoids which has reached most far towards the desired combination of high local but low systemic effects (results with this reference in rats — R. Brattsand et al.: Europ. J. Respir. Dis. 63 suppl. 122, 62, 1982; in man — S.Å. Johansson et al.: Europ. J. Respir. Dis. 63 Suppl. 122, 74, 1982).

The local anti-inflammatory activity of the compounds has been investigated as the potency to prevent ear edema according to the following procedure. Ear edemas were induced on male rats, weighing about 90 g, by application of 20 μ l/side of ear of 5% ethyl phenylpropionate (Aldrich Co.) dissolved in acetone. Two hours later the ear edema was measured with a special micrometer (Oditest, H.C. Kröplin, GmbH, Messzeug Fabrik). The glucocorticoids were applied as pretreatment 16 hours before induction of the edemas by application of 20 μ l/side of ear in solutions of acetone (0.08—250 μ g steroid/ml = 0.0064—20 μ g/rat). Six ears were tested per dose. The relative potency of the test compounds to prevent ear edemas was calculated with linear regression analysis in relation to the reference compound budesonide.

For the new compounds the doses used in the ear edema test do not induce systemic glucocorticoid actions. To be able to judge the systemic potency of the new compounds, they were administered in higher doses by the oral or intratracheal routes according to the following procedure. The sex and age of the rats were the same as described above. The glucocorticoids were suspended in a vehicle of CMC-Na 0.75 g, Tween® 80 0.04 g and NaCl 0.7% w/w ad 100 g. On oral administration the suspension was given by gavage in a volume of 0.5 ml. On intratracheal deposition the rats were lightly anaesthetized and were hanging on a slanted board and 0.1 ml was instilled in the trachea via the oropharynx. At least 5 doses were tested per compound within the range 40—10240 (oral) or 20—5120 μ g/rat (intratracheal route). Each dose group comprised 4 rats. The animals were killed after 4 days and the thymus weight recorded. The relative potency of the compounds was calculated by linear regression analysis in relation to the reference substance budesonide.

The results of the testing of glucocorticoids of the invention in accordance with the procedure given above are shown in Table 4. The table shows that the new compounds have surprisingly low systemic glucocorticoid activity of the same low magnitude as for hydrocortisone, while most new compounds have a much higher local anti-inflammatory potency than this reference. The compounds in example 2, 5, 7, 12, 13, 16 and 17 reach a much higher ratio between local and systemic glucocorticoid activities than what is recorded for budesonide and for hydrocortisone.

To effectively and safely treat inflammatory and allergic diseases of e.g. the airways or skin in large patient groups, there is a demand for compounds which possess sufficient local activity and an improved ratio between this local activity and the untoward systemic effects. The new compounds of this invention comply with these two claims at the same time.

Table 4. Local and systemic glucocorticoid effects of tested compounds

Example no.	Epimer	Local anti-inflammatory potency (LAIP)	Systemic glucocorticoid potency after		Therapeutic ratio between local and systemic potencies	
			oral adm. (SPO)	intratracheal adm. (SPI)	LAIP/SPO	TAIP/SPI
2	20R+S	0.20	0.02	0.02	10	10
3	20R+S	0.07	-	-	-	-
4	20R+S	0.07	-	-	-	-
5	20R+S	0.30	0.04	-	7.5	-
6	20R+S	0.05	-	-	-	-
7	20R+S	0.03	< 0.01	-	> 3	-
10	20R+S	0.11	-	-	-	-
11	20R+S	0.10	-	-	-	-
12	20R	0.30	0.03	0.02	10	15
13	20S	0.03	< 0.01	< 0.01	> 3	> 3
15	20S	0.03	-	-	-	-
16	20R	0.60	0.01	-	> 10	-
17	20R	2.00	< 0.10	-	≥ 20	-
Budesonide	22R+S	1	1	1	1	1
Hydrocortisone	-	0.0002	0.02	-	< 1	-

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Among the compounds of the present invention those described in example 2 (methyl (20RS)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate),

ex. 12 (methyl (20R)-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate),

ex. 5 (methyl (20RS)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate),

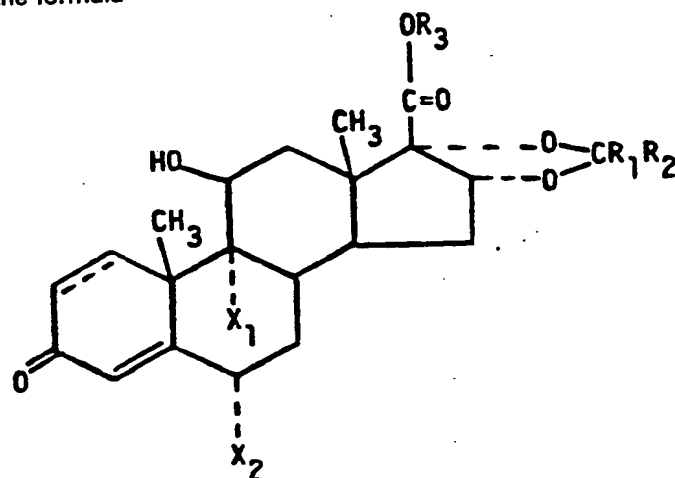
ex. 16 (methyl (20R)-9 α -fluoro-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate) and

ex. 17 (methyl (20R)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -propylmethylenedioxyandrosta-1,4-diene-3-one-17 β -carboxylate) are the preferred ones.

The 20R-epimer is the preferred epimer.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula



in the form of a stereoisomeric mixture or an epimer of the R or S type regarding the orientation of the substituents in the carbon atoms at position 20, in which formula the 1,2-position is saturated or is a double bond,

X₁ is hydrogen, fluorine, chlorine or bromine,

X₂ is hydrogen, fluorine, chlorine or bromine,

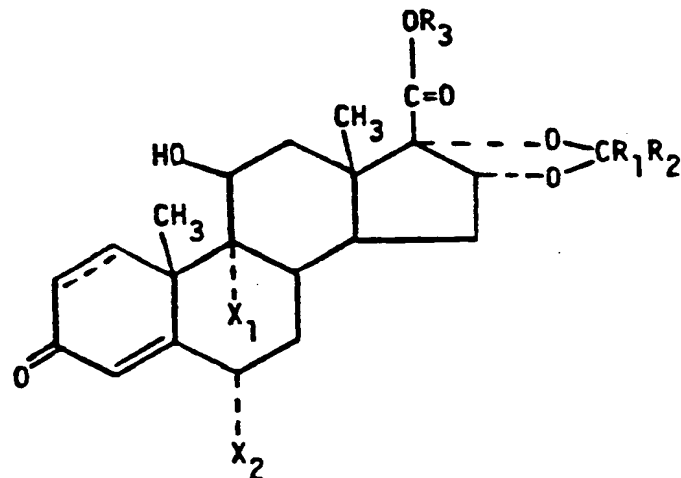
R₁ is hydrogen,

R₂ is a straight or branched hydrocarbon chain having 1—10 carbon atoms and

R₃ is a straight or branched chain alkyl group having 1—12 carbon atoms or an alkyl group having 1—5 carbon atoms substituted by 1—5 halogen atoms.

2. A steroid according to claim 1 in the form of the 20R-epimer.

3. A process for the preparation of a compound of the formula



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in the form of a stereoisomeric mixture or an epimer of the R or S type regarding the orientation of the substituents in the carbon atom at position 20, in which formula the 1,2-position is saturated or is a double bond,

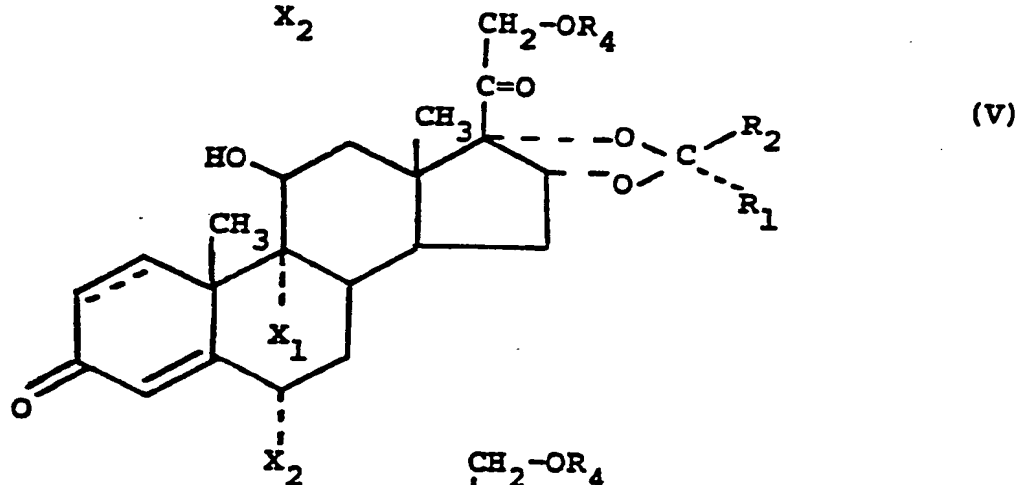
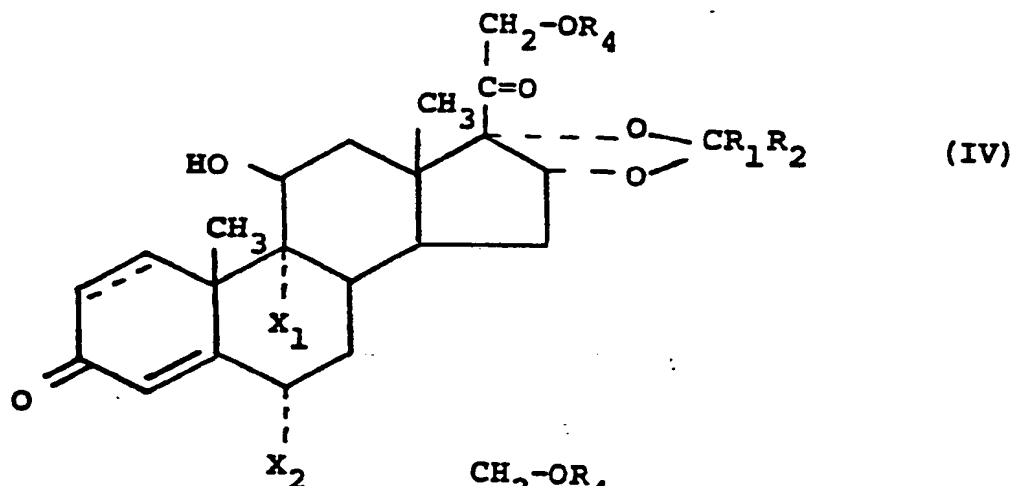
X_1 is hydrogen, fluorine, chlorine or bromine,

X_2 is hydrogen, fluorine, chlorine or bromine,

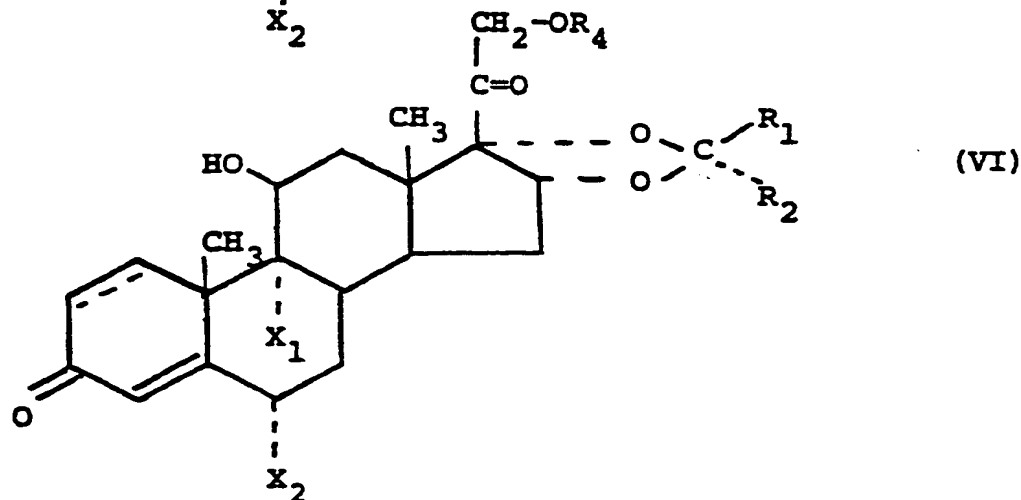
R_1 is hydrogen,

R_2 is a straight or branched hydrocarbon chain having 1—10 carbon atoms and

R_3 is a straight or branched chain alkyl group having 1—12 carbon atoms or an alkyl group having 1—5 carbon atoms substituted by 1—5 halogen atoms, characterized by oxidation of a compound of the formula



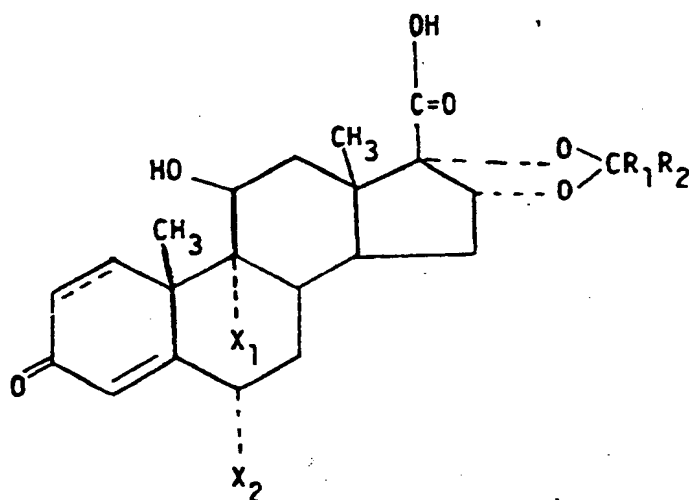
or



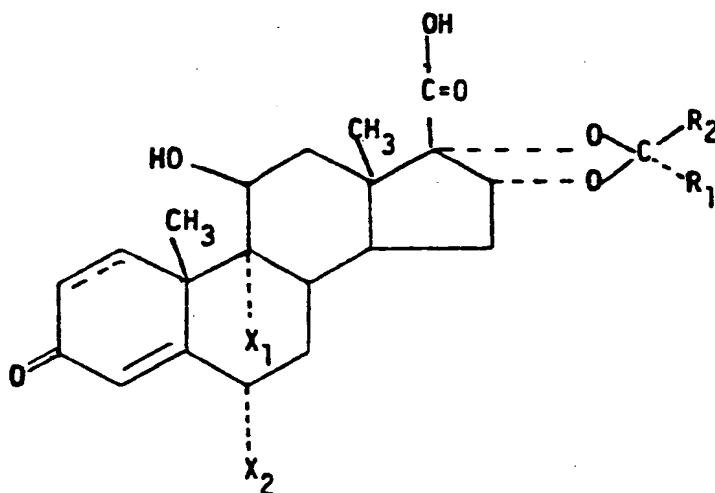
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wherein the solid and broken lines between C—1 and C—2 represent a single or double bond, X₁, X₂, R₁ and R₂ have the meaning given above and R₄ is hydrogen or a group —OC-alkyl, to the corresponding 17β-carboxylic acid, esterifying the thus obtained 17β-carboxylic acid and if the thus obtained ester is an epimeric mixture and a pure epimer is desired, resolving the mixture into the 20R and 20S epimers.

4. A process according to claim 3 characterized in that a compound according to claim 2 is prepared as a racemic mixture and a pure enantiomer.
5. A pharmaceutical preparation comprising as active ingredient a compound according to any of claims 1—2.
6. A pharmaceutical preparation according to claim 5 in dosage unit form.
7. A pharmaceutical preparation according to claims 5—6 comprising the active ingredient in association with a pharmaceutically acceptable carrier.
8. Use of a compound of the formula I according to claim 1 for the manufacture of medicaments with antiinflammatory action.
9. A compound according to any of claims 1—2 for use as an antiinflammatory drug.
10. Intermediates for the preparation of compounds of the formula I of claim 1 wherein R₃ is a straight or branched chain alkyl group having 1—12 carbon atoms, an alkyl group having 1—5 carbon atoms substituted by 1—5 halogen atoms, characterized by the formulas

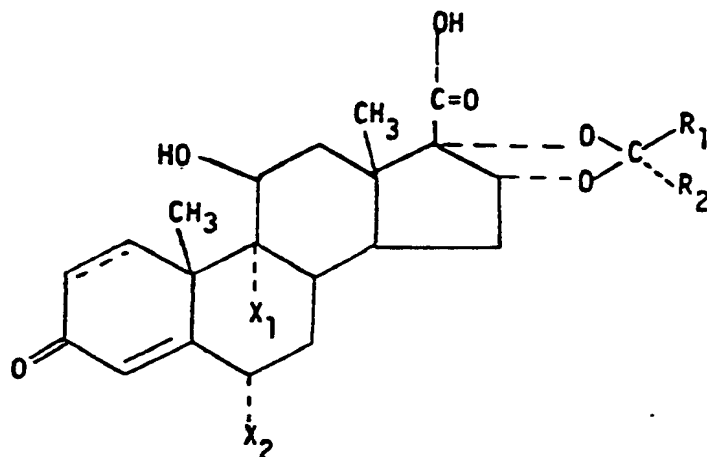


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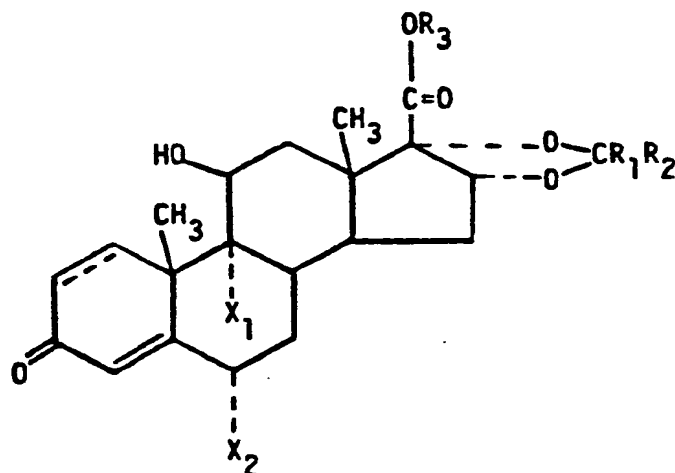
or



wherein the solid and broken lines between C—1 and C—2 represent a single or double bond,
X₁ is hydrogen, fluorine, chlorine or bromine,
X₂ is hydrogen, fluorine, chlorine or bromine,
R₁ is hydrogen,
R₂ is a straight or branched hydrocarbon chain having 1—10 carbon atoms.

Claims for the Contracting State: AT

1. A process for the preparation of a compound of the formula



(I)

in the form of a stereoisomeric mixture or an epimer of the R or S type regarding the orientation of the substituents in the carbon atoms at position 20, in which formula the 1,2-position is saturated or is a double bond,

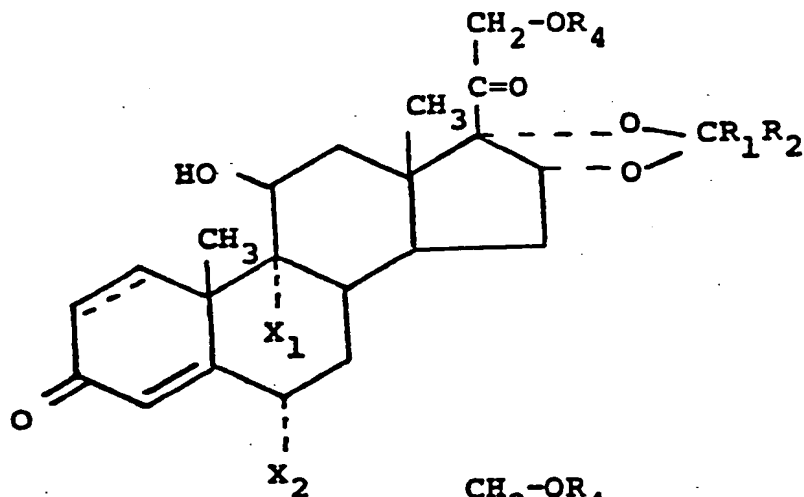
X₁ is hydrogen, fluorine, chlorine or bromine,

X₂ is hydrogen, fluorine, chlorine or bromine,

R₁ is hydrogen,

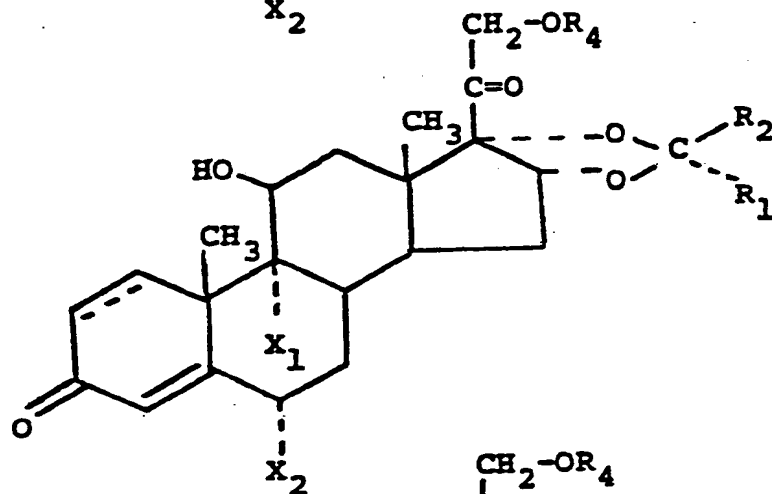
R₂ is a straight or branched hydrocarbon chain having 1—10 carbon atoms and

R₃ is a straight or branched chain alkyl group having 1—12 carbon atoms or an alkyl group having 1—5 carbon atoms substituted by 1—5 halogen atoms, characterized by oxidation of a compound of the formula



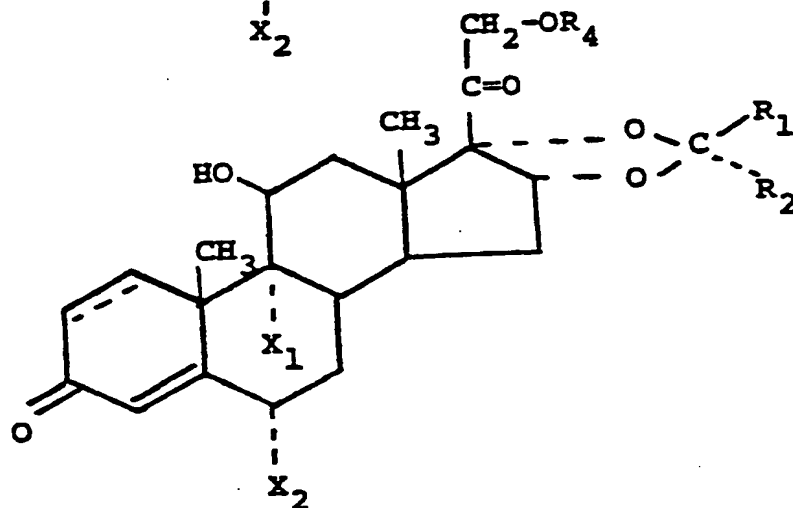
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or



(V)

or



(VI)

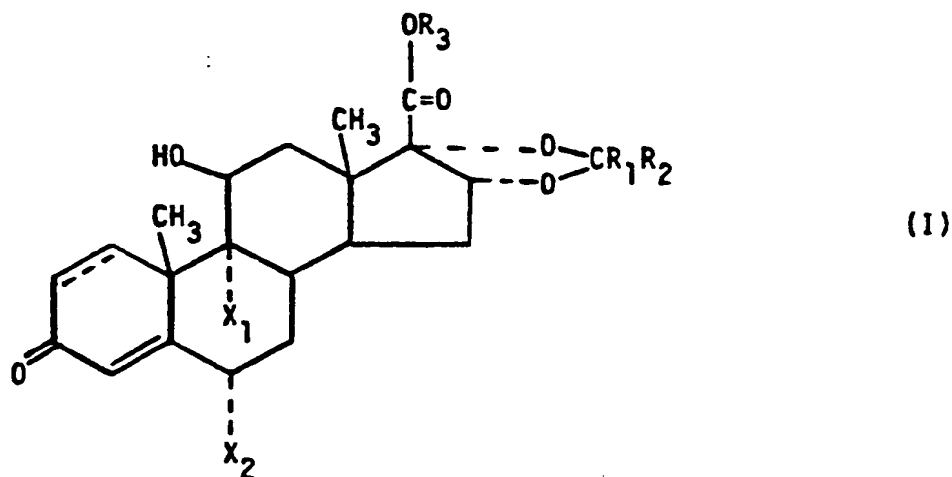
wherein the solid and broken lines between C—1 and C—2 represent a single or double bond, X_1 , X_2 , R_1 and R_2 have the meaning given above and R_4 is hydrogen or a group —OC-alkyl, to the corresponding 17β -carboxylic acid, esterifying the thus obtained 17β -carboxylic acid and if the thus obtained ester is an epimeric mixture and a pure epimer is desired, resolving the mixture into the 20R and 20S epimers.

2. A process according to claim 1 characterized in that the compound prepared is in the form of the 20R-epimer.

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Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der Formel



25 in Form einer Stereoisomerenmischung oder eines Epimeren vom R- oder S-Typ, was die Ausrichtung der Substituenten im Kohlenstoffatom an der Position 20 betrifft, in welcher Formel die 1,2-Position gesättigt oder eine Doppelbindung ist,

X₁ Wasserstoff, Fluor, Chlor oder Brom bedeutet,

X₂ Wasserstoff, Fluor, Chlor oder Brom darstellt,

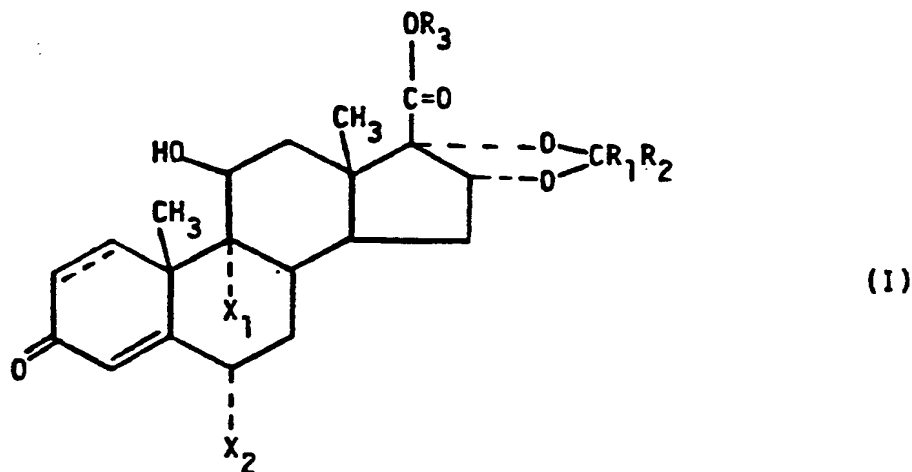
R₁ für Wasserstoff steht,

R₂ eine gerade oder verzweigte Kohlenwasserstoffkette mit 1—10 Kohlenstoffatomen ist und

R₃ eine gerad- oder verzweigt-kettige Alkylgruppe mit 1—12 Kohlenstoffatomen oder eine Alkylgruppe mit 1—5 Kohlenstoffatomen, die durch 1—5 Halogenatome substituiert sind, bedeutet.

2. Steroid nach Anspruch 1 in Form des 20R-Epimeren.

3. Verfahren zur Herstellung einer Verbindung der Formel



55 in Form einer Stereoisomerenmischung oder eines Epimeren vom R- oder S-Typ, was die Ausrichtung der Substituenten im Kohlenstoffatom an der Position 20 betrifft, in welcher Formel die 1,2-Position gesättigt oder eine Doppelbindung ist,

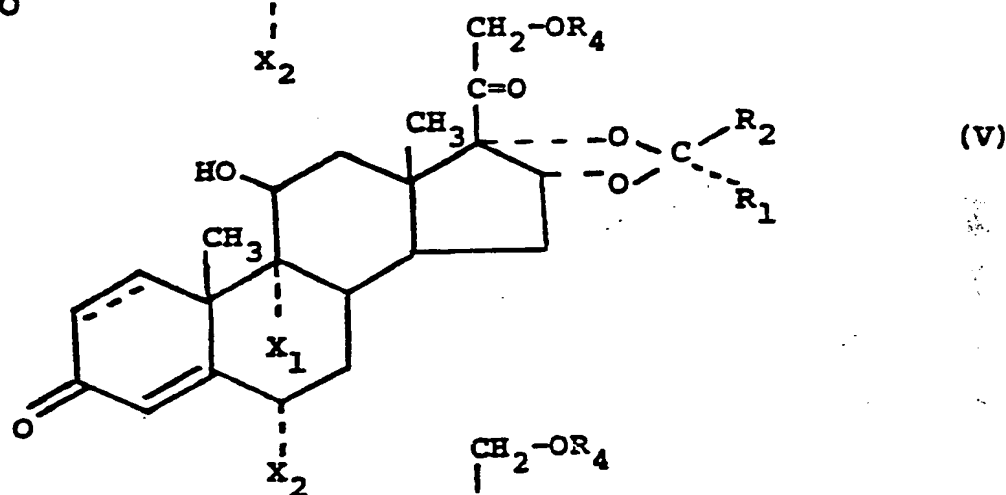
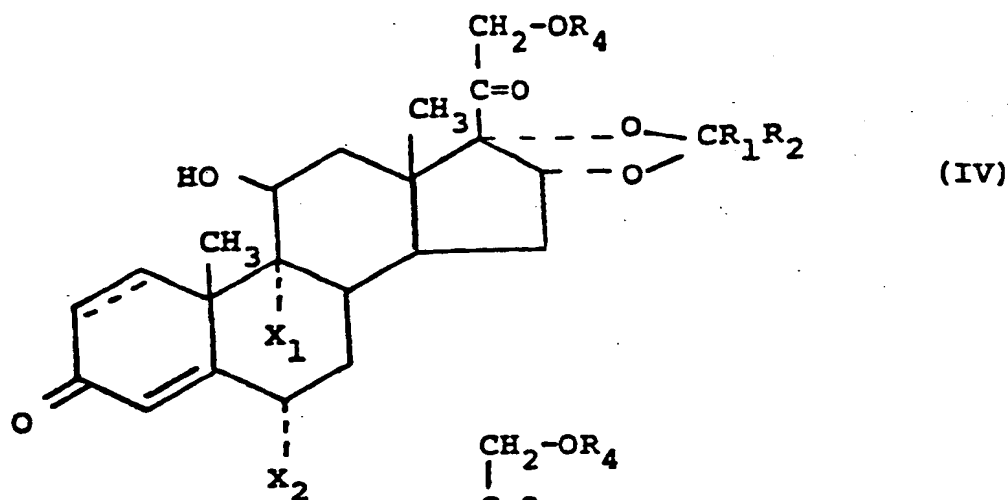
X₁ Wasserstoff, Fluor, Chlor oder Brom bedeutet,

X₂ Wasserstoff, Fluor, Chlor oder Brom darstellt,

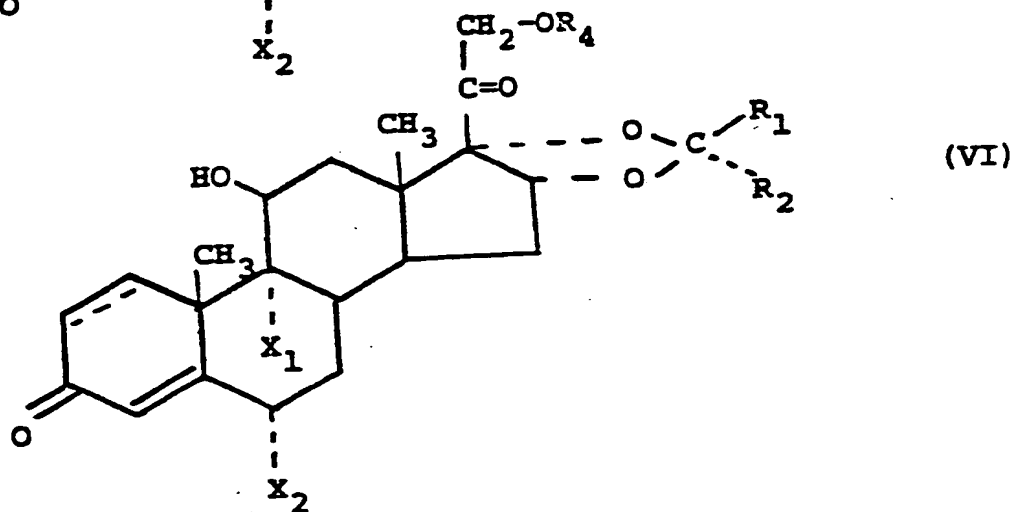
R₁ für Wasserstoff steht,

R₂ eine gerade oder verzweigte Kohlenwasserstoffkette mit 1—10 Kohlenstoffatomen ist und

R₃ eine gerad- oder verzweigt-kettige Alkylgruppe mit 1—12 Kohlenstoffatomen oder eine Alkylgruppe mit 1—5 Kohlenstoffatomen, die durch 1—5 Halogenatome substituiert sind, bedeutet, gekennzeichnet durch die Oxidation einer Verbindung der Formel



oder



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worin die durchgehenden und strichlierten Linien zwischen C—1 und C—2 eine Einfach- oder Doppelbindung darstellen, X₁, X₂, R₁ und R₂ die oben angegebene Bedeutung haben und R₄ für Wasserstoff oder eine Gruppe —OC-Alkyl steht, zur entsprechenden 17β-Carbonsäure, Veresterung der so erhaltenen 17β-Carbonsäure, und wenn der so erhaltene Ester eine Epimerenmischung ist und ein reines Epimeres erwünscht ist, die Auftrennung der Mischung in die 20R- und 20S-Epimeren.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß eine Verbindung nach Anspruch 2 hergestellt wird.

5. Pharmazeutische Präparation, welche als aktives Ingrediens eine Verbindung nach einem der Ansprüche 1—2 umfaßt.

6. Pharmazeutische Präparation nach Anspruch 5 in Dosiseinheitsform.

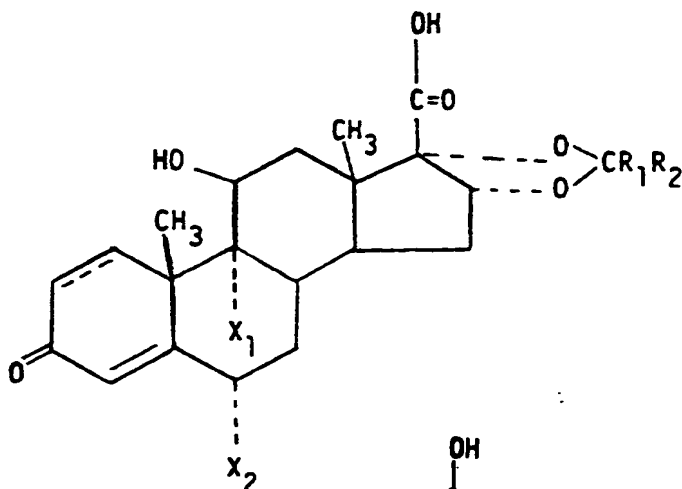
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7. Pharmazeutische Präparation nach den Ansprüchen 5—6, welche das aktive Ingrediens in Verbindung mit einem pharmazeutisch akzeptablen Träger umfaßt.

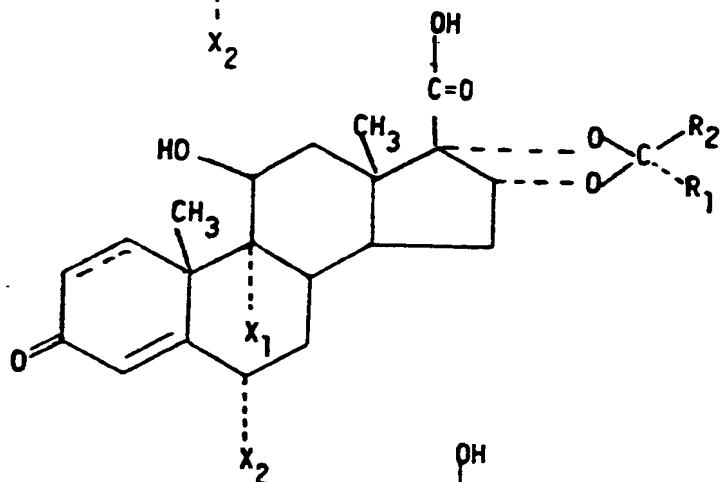
8. Verwendung einer Verbindung der Formel I nach Anspruch 1 zur Herstellung von Medikamenten mit entzündungshemmender Wirkung.

9. Verbindung nach einem der Ansprüche 1—2 zur Verwendung als entzündungshemmende Droge.

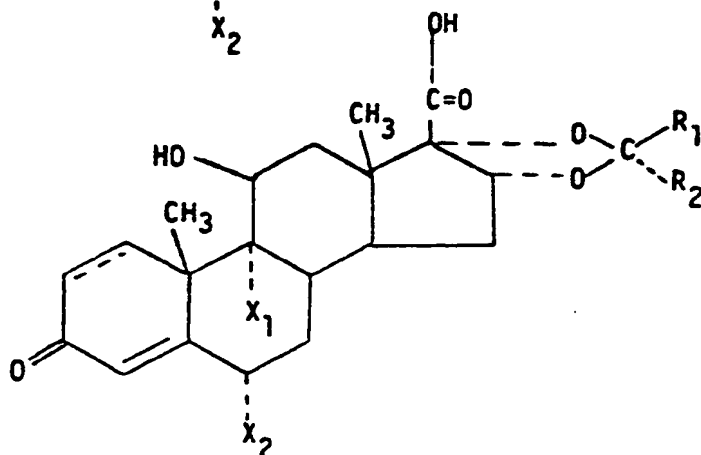
10. Zwischenprodukte für die Herstellung von Verbindungen der Formel I des Anspruchs 1, worin R_3 eine geradoder verzweigt-kettige Alkylgruppe mit 1—12 Kohlenstoffatomen, eine Alkylgruppe mit 1—5 Kohlenstoffatomen, die durch 1—5 Halogenatome substituiert sind, bedeutet, gekennzeichnet durch die Formeln



oder



oder



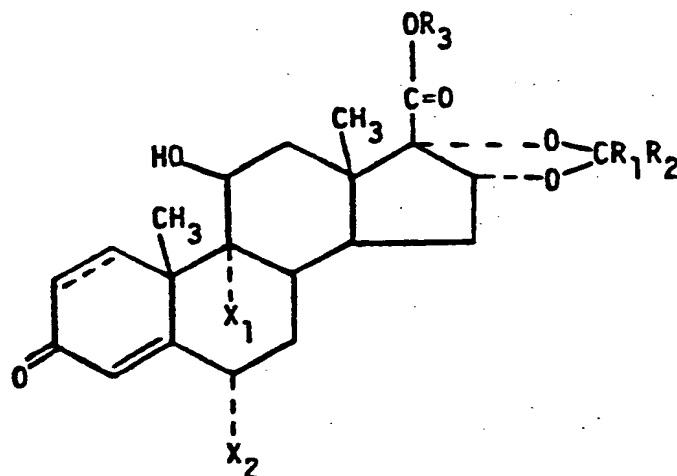
worin die durchgehenden und strichlierten Linien zwischen C—1 und C—2 eine Einfach-oder Doppelbindung darstellen, X_1 Wasserstoff, Fluor, Chlor oder Brom bedeutet,

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X_2 Wasserstoff, Fluor, Chlor oder Brom ist,
 R_1 für Wasserstoff steht,
 R_2 eine gerade oder verzweigte Kohlenwasserstoffkette mit 1—10 Kohlenstoffatomen ist.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel



(I)

in Form einer Stereoisomerenmischung oder eines Epimeren vom R- oder S-Typ, was die Ausrichtung der Substituenten im Kohlenstoffatom an der Position 20 betrifft, in welcher Formel die 1,2-Position gesättigt oder eine Doppelbindung ist,

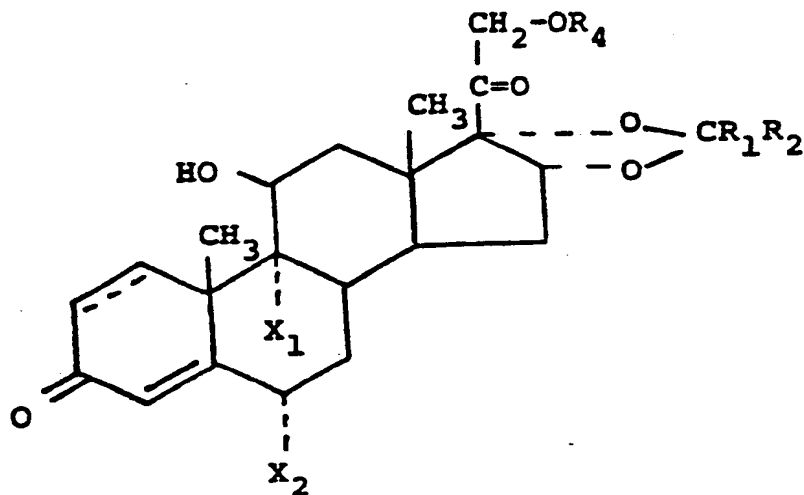
X_1 Wasserstoff, Fluor, Chlor oder Brom bedeutet,

X_2 Wasserstoff, Fluor, Chlor oder Brom darstellt,

R_1 für Wasserstoff steht,

R_2 eine gerade oder verzweigte Kohlenwasserstoffkette mit 1—10 Kohlenstoffatomen ist und

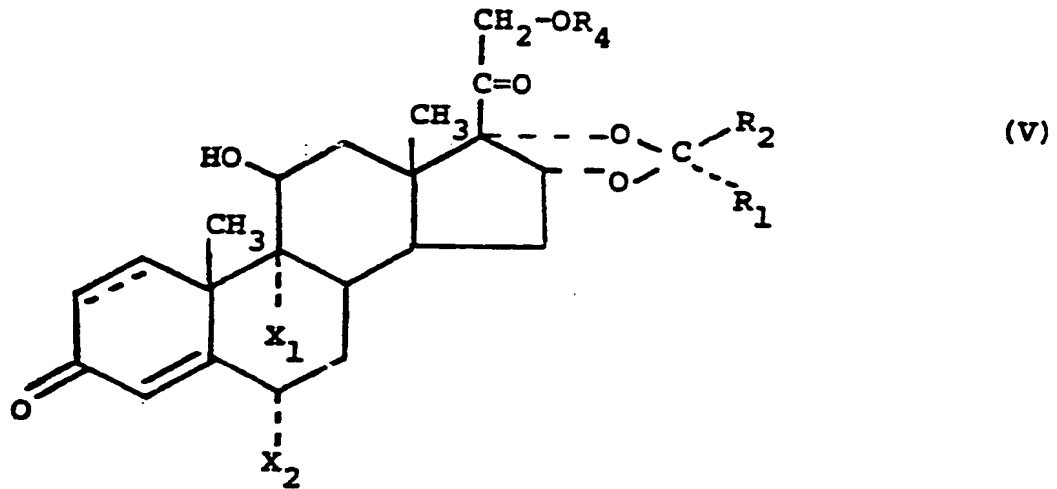
R_3 eine gerad- oder verzweigtkettige Alkylgruppe mit 1—12 Kohlenstoffatomen oder eine Alkylgruppe mit 1—5 Kohlenstoffatomen, die durch 1—5 Halogenatome substituiert sind, bedeutet gekennzeichnet durch die Oxidation einer Verbindung der Formel



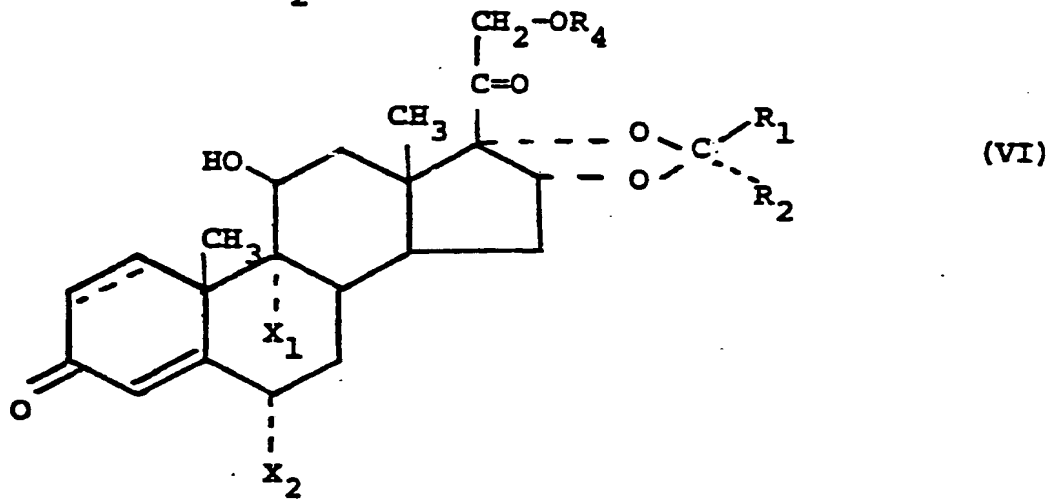
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oder

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oder

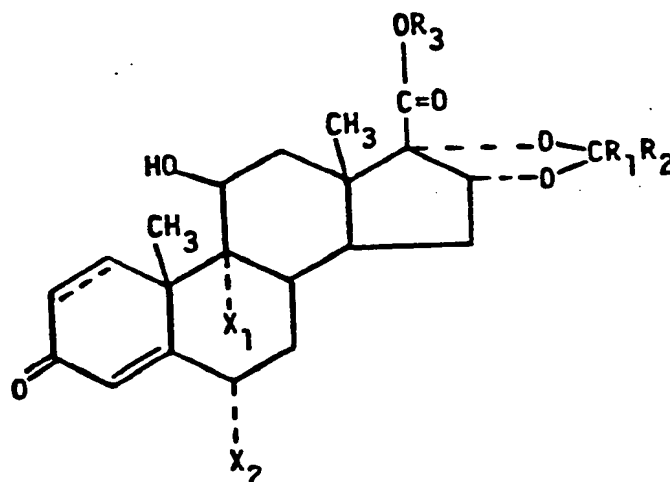


worin die durchgehenden und strichlierten Linien zwischen C—1 und C—2 eine Einfach- oder Doppelbindung darstellen, X₁, X₂, R₁ und R₂ die oben angegebene Bedeutung haben und R₄ für Wasserstoff oder eine Gruppe —OC-Alkyl steht, zur entsprechenden 17β-Carbonsäure, Veresterung der so erhaltenen 17β-Carbonsäure, und wenn der so erhaltene Ester eine Epimerenmischung ist und ein reines Epimeres erwünscht ist, die Auftrennung der Mischung in die 20R- und 20S-Epimeren.

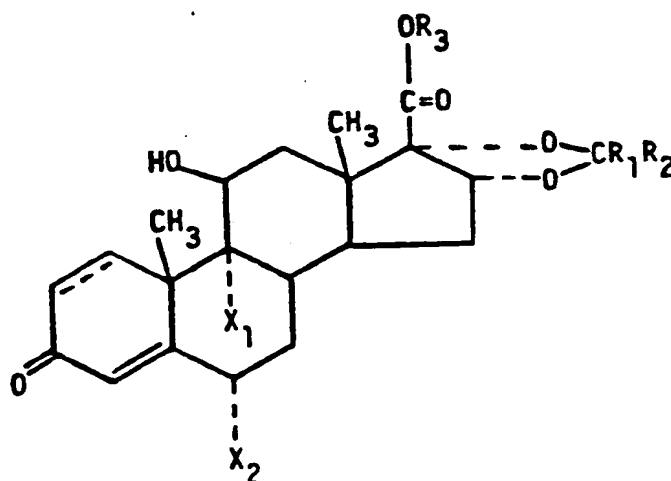
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die hergestellte Verbindung in Form des 20R- Epimeren vorliegt.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

(1)



3. Procédé pour la préparation d'un composé de formule



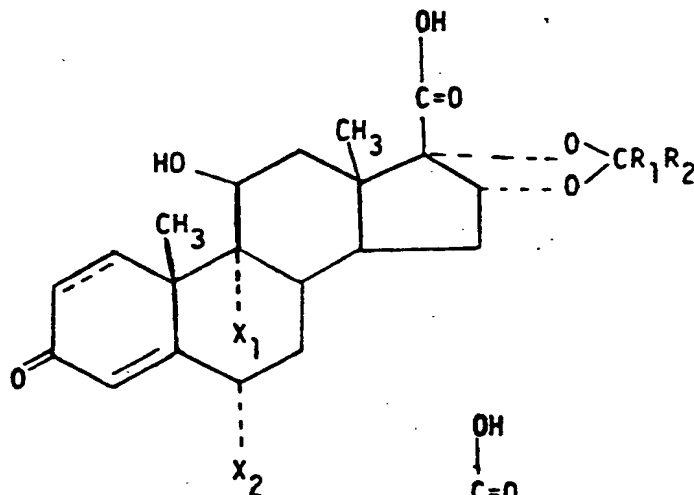
R₂ représente une chaîne hydrocarbonée linéaire ou ramifiée ayant 1 à 10 atomes de carbone, et
R₃ représente un groupe alkyle linéaire ou ramifié ayant 1 à 12 atomes de carbone ou un groupe alkyle

ayant 1 à 5 atomes de carbone et comportant 1 à 5 atomes d'halogène(s) comme substituant(s), procédé caractérisé par l'oxydation d'un composé de formule

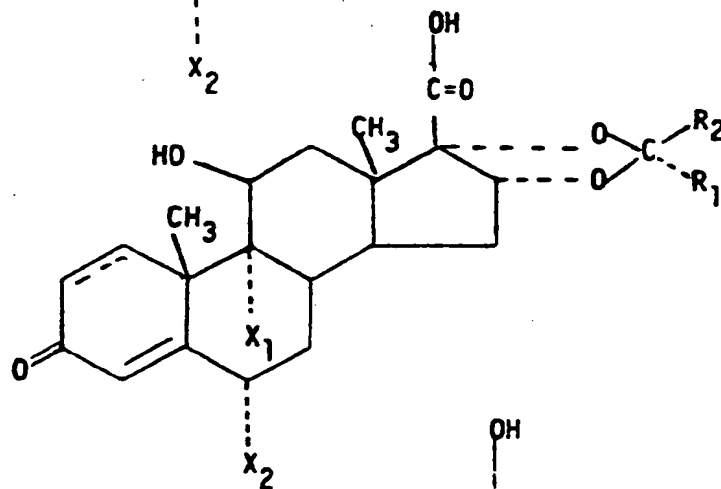
R_4 représente un atome d'hydrogène ou un groupe —OC-alkyle, pour obtenir l'acide 17 β carboxylique correspondant, l'estérification de l'acide 17 β -carboxylique ainsi obtenu et, si l'ester ainsi obtenu est un mélange d'épimères et si l'on désire un épimère pur, la résolution du mélange en les épimères 20R et 20S.

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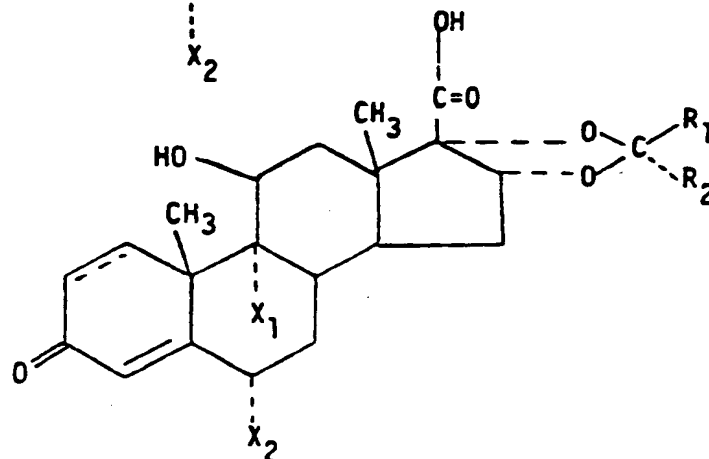
4. Procédé selon la revendication 3, caractérisé en ce qu'on prépare un composé selon la revendication 2.
5. Préparation pharmaceutique comprenant, comme ingrédient actif, un composé selon l'une quelconque des revendications 1—2.
6. Préparation pharmaceutique selon la revendication 5, sous forme de doses unitaires.
7. Préparation pharmaceutique selon les revendications 5—6, comprenant l'ingrédient actif en association avec un excipient ou véhicule pharmaceutiquement acceptable.
8. Utilisation d'un composé de formule I selon la revendication 1 pour la fabrication de médicaments doués d'une action anti-inflammatoire.
9. Composé selon l'une quelconque des revendications 1—2, destiné à servir de produit anti-inflammatoire.
10. Intermédiaires pour la préparation de composés de formule I de la revendication 1 (dans laquelle R_3 représente un groupe alkyle linéaire ou ramifié atant 1 à 12 atomes de carbone ou un groupe alkyle ayant 1 à 5 atomes de carbone et substitué par 1 à 5 atomes d'halogène(s), caractérisés par les formules



ou



ou

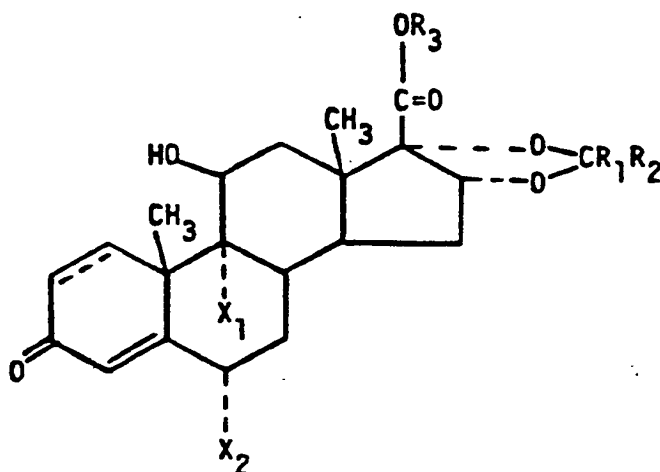


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dans lesquelles les lignes pleines ou brisées entre C—1 et C—2 représentent une liaison simple ou double;
 X_1 représente un atome d'hydrogène, de fluor, de chlore ou de brome;
 X_2 représente un atome d'hydrogène, de fluor, de chlore ou de brome;
 R_1 représente un atome d'hydrogène;
 R_2 représente un chaîne hydrocarbonée linéaire ou ramifiée ayant 1 à 10 atomes de carbone.

Revendications pour l'Etat contractant: AT

1. Procédé pour la préparation d'un composé de formule



(I)

sous a forme d'un mélange de stéréoisomères ou d'un épimère du type R ou S concernant l'orientation des substituants fixés sur l'atome de carbone en position 20, formule dans laquelle la position 1—2 est saturée ou présente une double liaison;

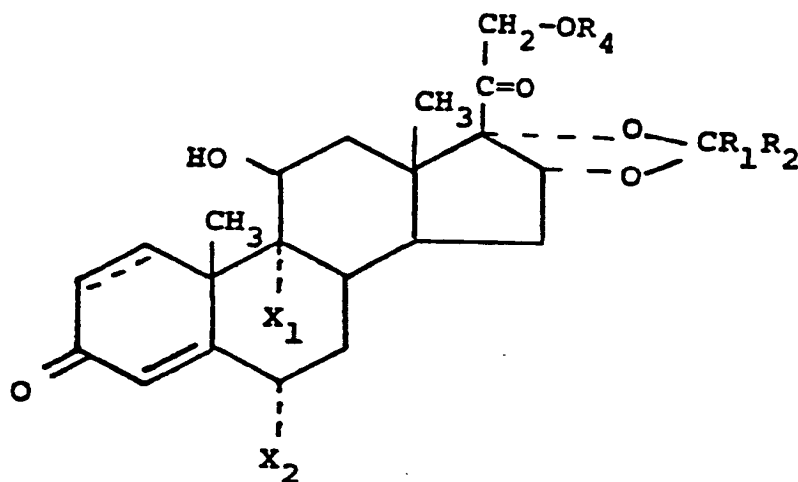
X_1 représente un atome d'hydrogène, de fluor, de chlore ou de brome;

X_2 représente un atome d'hydrogène, de fluor, de chlore ou de brome;

R_1 représente un atome d'hydrogène;

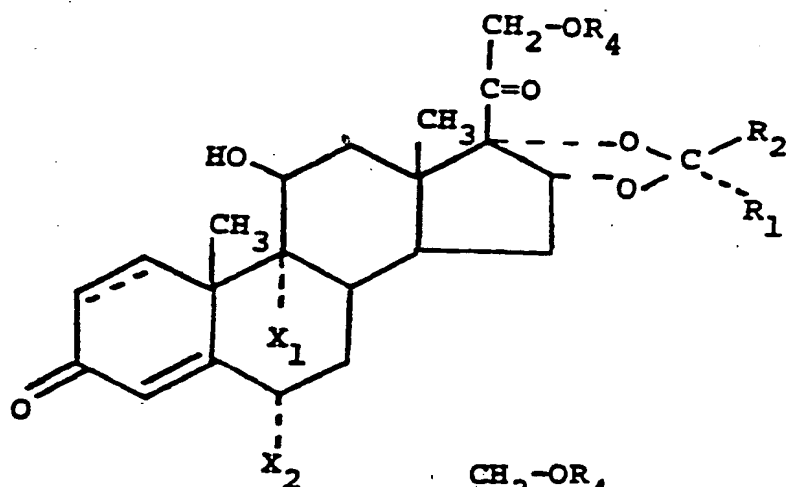
R_2 représente un chaîne hydrocarbonée linéaire ou ramifiée ayant 1 à 10 atomes de carbone, et

R_3 représente un groupe alkyle linéaire ou ramifié ayant 1 à 12 atomes de carbone ou un groupe alkyle ayant 1 à 5 atomes de carbone et substitué par 1 à 5 atomes d'halogène(s), procédé caractérisé par l'oxydation d'un composé de formule:

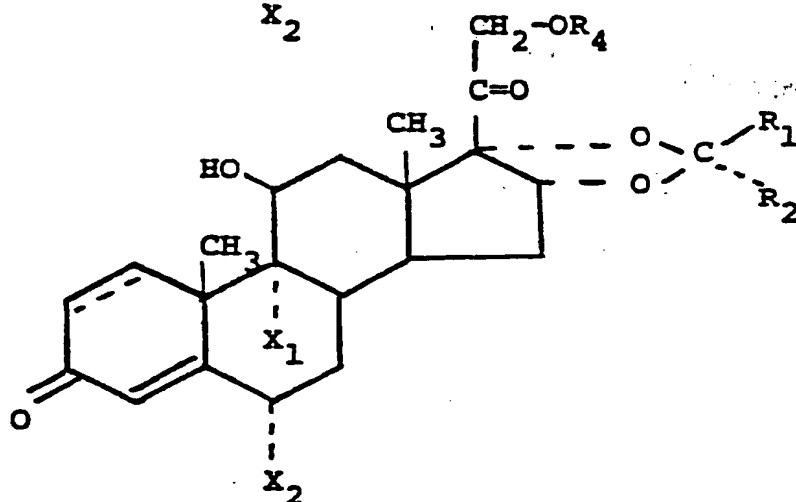


(IV)

ou



(v)



(VI)

dans lesquelles les lignes pleines et brisées entre C—1 et C—2 représentent une liaison simple ou double;
X₁, X₂, R₁ et R₂ ont les sens indiqué ci-dessus et

R₄ représente un atome d'hydrogène ou un groupe —OC-alkyle, pour obtenir l'acide 17β-carboxylique, l'estérification de l'acide 17β-carboxylique ainsi obtenu et, si l'ester ainsi obtenu est un mélange d'épimères et si l'on désire un épimère pur, la résolution du mélange en les épimères 20R et 20S.

2. Procédé selon la revendication 1, caractérisé en ce que le composé préparé est sous la forme de l'épimère 20R.

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